for mass spectral discussions.

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Potential Antitumor Agents. 20. Structure–Activity–Site Relationships for the 4'-(9-Acridinylamino)alkanesulfonanilides

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A series of 87 L1210 active 4'-(9-acridinylamino)alkanesulfonanilides has been screened against L1210 cells (10^5) implanted at various sites (ip, sc, ic) employing early ip drug administration for a limited time. With each implantation site a different most active congener was selected. For good activity against tumor implanted remotely from the ip drug administration site, an agent should be more lipophilic than that found optimal for ip implanted tumor. An acridine 4-CH_3 group appears to assist drug translocation, possibly by sterically hindering binding to nonproductive sites. An unprotected NH_2 group on the acridine ring system is incompatible with activity against sc implanted tumor. Agents in which NH_2 is shielded by N-acetylation, N-monomethylation, or ortho substitution with a bulky group can inhibit sc implanted tumor.

Depending on the target disease process the chemotherapeutic agent which is selected from a range of congeners for clinical trial must have certain necessary properties. Inevitably reasonable efficacy in animal screening tests is demanded. Intrinsic physical, chemical, pharmacologic, or toxicologic properties of that selected agent may prove such as to force selection of a different congener which, although significantly less active in a screening test, has more desirable alternate features for clinical application. This is particularly true in cancer chemotherapy where, in striving for cure, we must aim for total tumor cell eradication.[1-3] To have curative potential against the advanced disease, agents must be able to distribute in effective concentration to all cancer cells. In analyzing the structure–activity relationships (SAR) of the acridylmethanesulfonanilide series, we have generated several hundred tumor-active congeners.[4-9] Screening in these studies has employed early intraperitoneal (ip) treatment of ip implanted L1210. We have now attempted to develop simple screening type tests which will demonstrate those molecular features which provide favorable drug disposition patterns, as well as those which contribute to high intrinsic selectivity toward target tumor cells. From such information it was hoped it would be possible to select structural components common to both sets and, from these, generate agents with desirable clinical attributes.

The research described examines the comparative effectiveness of certain earlier prepared agents against depots of L1210 leukemia implanted at different anatomic sites. Early drug dosage for a strictly limited period has been employed so that observed life extensions may reflect primarily effects against the initial tumor depot, rather than the widely disseminated disease that is combated when treatment is either late or protracted. To probe further our initial findings in this study, an extensive range of new congeners has been prepared and evaluated in these modified screening systems. Certain structure–activity–site relationships are presented.

Chemistry. Most synthetic steps necessary in agent generation have been dealt with earlier in full.[4-9] The overall route requires generation of an *N*-arylanthranilic acid[6] and, following ring closure ($POCl_3$, H_2SO_4, PPA, PPE)[9] to a 9(10*H*)-acridone, then conversion of this ($POCl_3$, $SOCl_2$–DMF)[6] to a 9-chloroacridine. Final mild acid catalyzed coupling of the 9-chloroacridines and a 4'-aminosulfonanilide component provides agents.[4-9] To avoid troublesome isomer separation following the ring closure step acridones have been prepared, where possible, by unequivocal routes. For example, Ullmann condensation[6,10] of 2,4-dichlorobenzoic acid and 4-nitroaniline provided a substituted *N*-arylanthranilic acid which on ring closure provided as sole product the 3-chloro-7-nitroacridone necessary for **65** (Table II). Similar steps from 2,4-dichloro-5-nitrobenzoic acid and aniline provided the isomeric 3-chloro-2-nitroacridone required for **67**. The formulas of the intermediary *N*-arylanthranilic acids quoted in the Experimental Section specify the 2-halobenzoic acid and aniline components utilized in Ullmann condensations.

Side-chain intermediates for **42–44** were prepared by acylation of *N*-(4-amino-2-methoxyphenyl)butanamide[7] with the requisite sulfonyl chloride and then hydrolytic (H^+) removal of the protecting butyryl function.

Acylation (*o*-phenylenephosphorochloridite–RCOOH)[6] of the corresponding 3-NH_2 compound provided **45** and **46**. Most variants containing primary amino groups (**57, 66, 68, 70**) were prepared by terminal reduction (Fe/H^+) of the corresponding nitro compounds. Certain amine variants were more conveniently prepared from the acetylamino derivatives. This was the case with the 2-amino-3-trifluoromethyl analogue **70**; initial preparation

by reduction of the corresponding nitro compound **69** gave a difficultly purified product and a resultant low yield. Nitro group reduction at the acridone stage ($SnCl_2$–HCl),[6] N-acetylation of the formed amine, and then reaction of the derived 9-chloroacridine with amine component in the usual manner provided the 2-acetylamino analogue which was immediately hydrolyzed to provide a superior yield of **70**.

Bromination of 3-methylacetanilide furnished 2,4-dibromo-5-methylacetanilide and a following oxidation of ring methyl group ($KMnO_4$) provided 2,4-dibromo-5-acetylaminobenzoic acid. Ullmann condensations employing this dibromo acid and aniline or *o*-toluidine provided *N*-arylanthranilic acids which, on ring closure, provided the 2-acetylamino-3-bromoacridones necessary for synthesis of **71–73**. Following conversion to the corresponding 9-chloroacridines[6] these were coupled with the requisite aniline component and the protecting acetyl function was immediately removed by acid hydrolysis. Using polyphosphate ester[12] as acridone ring closure reagent (100 °C, 2 h), there is minimal hydrolytic cleavage of acetylamino precursors.

Initially 3-methylaminoacridone was prepared by use of 3-(*N*-methylbenzenesulfonamido)aniline in Ullmann condensations and obvious further steps. Use of the same amine component and methyl *o*-cresotinate in the Chapman rearrangement[9,11] route provided an *N*-arylanthranilic acid necessary for preparation of 3-methylamino-5-methylacridone. Later, 2-chloro-4-(*N*-methylbenzenesulfonamido)benzoic acid was prepared and utilization of this in Ullmann condensations provided a much more convenient route to the *N*-arylanthranilic acids necessary as precursors for **58–64**. Conveniently, acridone ring closure of *N*-arylanthranilic acids containing an *N*-methylbenzenesulfonamide function with polyphosphoric acid (100 °C for 2 h and then 140 °C for 1 h) cleanly removed the protecting benzenesulfonyl group.

Attempted preparation of 3-dimethylaminoacridine variants by equivalent routes has been unsuccessful. While 3-dimethylaminoacridone could be prepared, all attempts to convert this to the corresponding 9-chloro compound have produced red-purple gums which TLC demonstrates to be complex mixtures. 9-Chloroacridine will itself react with electron-rich aromatic components, e.g., *N*,*N*-dimethylaniline,[13,14] to provide in this case 9-(4-dimethylaminophenyl)acridine which has a purple monocation. We suggest that when there is a sufficiently strong electron-donor component attached to an acridone, attempted conversion to the 9-chloro compound may initiate self-condensation with production of colored polymers.

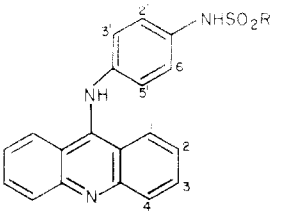
As before, it was necessary to use the Chapman rearrangement[9,11] to obtain acceptable yields of intermediates for preparation of acridones containing both 4- and 5-substituents.

Biologic Testing. To ensure reproducibility in screening tests every effort has been made to obtain water-soluble drug formulations.[6] In most cases the hydrochloride or methanesulfonate salts (see Tables I and II) have proved sufficiently water soluble. The analogues bearing nitro functions are extremely insoluble and have had to be administered as homogenized suspensions in aqueous methylcellulose. While dose–antileukemic activity profiles in ip L1210 tests for soluble drug formulations can be confidently accumulated over considerable time periods, we have found for insoluble drugs that the following approach provides more reproducible maximum life extensions. After preliminary screening tests, to indicate activity and permissible dosage levels, a dilution series of a single drug suspension has been screened at one time in a single group of tests, ensuring that the highest dose was toxic and the lowest suboptimal.

The same dosage schedule, ip qd 1–5 days, and tumor inoculum (10^5 cells) have been employed in all L1210 tests: intraperitoneal (ip), subcutaneous (sc), and intracerebral (ic). In sc and ic L1210 assays a series of drug dilutions providing small dose intervals (0.18 log dose) has been screened on one occasion, the median dose being the optimum observed in earlier ip L1210 assays. For acceptance of test results with a single compound the highest dose must provide evidence of drug toxicity as shown by premature animal deaths or lessened levels of life extension in comparison with those seen at lower doses. The lowest dose of the dilution series must be clearly suboptimal, as evidenced by shorter life extension than seen with higher doses or clear average body weight gain. As necessary, screening was repeated until, in one batch of tests, a drug dilution series provided acceptable spanning of the optimum drug dose.

The life spans of animals receiving a standard 10^5 tumor cells inoculum ip, sc, or ic are different, ca. 9.5, 11, and 8 days, respectively, in our C_3HxDBA_2 F_1 hybrid mice. Caution is necessary when intercomparing percentage life extensions obtained under the different test conditions.

Structure–Activity–Site Relationships. Based on earlier experience our approach to unraveling the SAR of these acridines was to investigate the changes in biologic activity within the homologous 4′-(9-acridinylamino)alkanesulfonanilides (**1**).[6] The observed activity changes



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were interpreted as due to altering molecular lipophilic–hydrophilic balance and utilized as reference data to compensate for the effects due to changes in this factor in varyingly substituted congeners.[6,7] As before, the R_m values of drug cations, from reversed phase partition chromatography, have been employed as measures of lipophilic–hydrophilic balance.[8,9]

Subcutaneous L1210. Those members of the initial reference homologous series active against early ip L1210 (**2–4**, Table I) when screened against sc implanted L1210 provided considerably shorter life extensions, but there was also a different order in the activities observed. As the lipophilic character of the parent agent **2** is increased, to provide **3**, activity against ip L1210 decreases while activity against sc tumor increases. Although most of the life extensions observed against sc tumor are relatively small, they can be readily reproduced. Markedly longer life extensions may be gained by protracted treatment[24] but, for the reasons stated earlier, this could defeat the objects of this study. A further example of the same effect is provided by the homologous series (**5–9**); this is less clear-cut for the first two members (**5, 6**) but between **5** and **7** there is a decrease in ip activity which is not seen with the sc tumor. Similarly, in an homologous series bearing the generally dose potency increasing 3′-OCH_3,[9] the high ip activity of the parent (**20**) drops with increasing lipophilic character (**42, 43**) but in the same series activity against sc tumor increases. Again, between **5** and **46** there is a pronounced drop in ip L1210 effectiveness not seen

Table I. Antitumor Screening Results Employing L1210 Implanted at Different Sites

No.	R in 1	Ref	Formulation[a]	R_m[b]	ΔpK_a[c]	O.D.[d]	L1210 ILS, %[e] ip	sc	ic
2	CH_3	6	MsOH	0.00	0.0	45	107	28	–[f]
3	CH_2CH_3	6	MsOH	0.20	0.0	55	71	41	–
4	$(CH_2)_2CH_3$	6	MsOH	0.39	0.0	250	29	27	–
5	CH_3, 3-$NHCOCH_3$	6	MsOH	−0.12	0.0	13	114 (2)	33	–
6	CH_2CH_3, 3-$NHCOCH_3$	6	MsOH	0.07	0.0	27	173	48	27
7	$(CH_2)_2CH_3$, 3-$NHCOCH_3$	6	MsOH	0.26	0.0	26	97	36	–
8	$(CH_2)_3CH_3$, 3-$NHCOCH_3$	6	MsOH	0.45	0.0	25	43	–	
9	$(CH_2)_4CH_3$, 3-$NHCOCH_3$	6	MsOH	0.64	0.0	37	–		
10	CH_3, 2-NH_2	6	HCl	−0.31	+0.4	25	78	–	
11	CH_3, 3-OCH_3	6	MsOH	0.06	+0.1	17	117	37	–
12	CH_3, 3-Cl	6	HCl	0.13	−0.7	75	103	41	27
13	CH_3, 3-NO_2	6	HCl-B	−0.07	−2.1	25	123 (2)	43	–
14	CH_3, 3-NH_2	6	HBr	−0.17	+1.5	2.5	81 (1)	–	
15	CH_3, 3-Br	6	HCl	0.14	−0.7	35	65	40	27
16	CH_3, 3-CH_3	6	MsOH	0.11	+0.2	17	117	36	–
17	CH_3, 4-CH_3	6	MsOH	0.06	+0.2	33	113	52	34
18	CH_3, 4-OCH_3	6	HCl	0.01	−0.1	75	81	36	26
19	CH_3, 3,4-$(CH_3)_2$	6	MsOH	0.14	+0.4	50	91 (1)	49	31
20	CH_3, 3'-OCH_3	7	MsOH	0.18	0.0	6.7	114 (2)	27	–
21	CH_3, 3'-CH_3	7	MsOH	0.21	0.0	97	106	39	29
22	CH_3, 3'-OCH_3, 3-Cl	7	HCl	0.31	−0.7	10	72	36	–
23	CH_3, 3'-OCH_3, 3-CH_3	7	MsOH	0.29	+0.2	4	88	29	–
24	CH_3, 3'-OCH_3, 4-CH_3	7	MsOH	0.24	+0.2	6	111	47	31
25	CH_3, 3'-OCH_3, 3-NO_2	9	HCl-B	0.11	−2.1	4.5	84	41	–
26	CH_3, 3-NO_2, 5-CH_3	9	HCl-B	−0.01	−1.9	100	113 (2)	98 (2)	–
27	CH_3, 3'-OCH_3, 3-NO_2, 5-CH_3	9	HCl-B	0.17	−1.9	11	107 (1)	78	–
28	CH_3, 3-NO_2, 6-CH_3	9	HCl-B	0.04	−1.9	>500	99[g]	29[g]	–
29	CH_3, 3-NO_2, 6-CH_3, 3'-OCH_3	9	HCl-B	0.23	−1.9	50	91	54	–
30	CH_3, 3-NO_2, 5,6-$(CH_3)_2$	9	HCl-B	0.07	−1.7	150	103 (1)	91 (1)	–
31	CH_3, 3-NO_2, 5,6-$(CH_3)_2$, 3'-OCH_3	9	HCl-B	0.27	−1.7	35	92 (1)	98 (1)	–
32	CH_3, 3-NH_2, 3'-OCH_3	9	HCl	0.01	+1.5	6	82	–	
33	CH_3, 3-$NHCOCH_3$, 3'-OCH_3	9	HCl	0.06	0.0	24	89 (1)	36	–
34	CH_3, 3-NH_2, 3'-CH_3	9	HCl	0.04	+1.5	37	108 (2)	–	
35	CH_3, 3-$NHCOCH_3$, 3'-CH_3	9	HCl	0.11	0.0	55	107 (2)	27	–
36	CH_3, 3-NH_2, 5-CH_3	9	HCl	−0.11	+1.7	2	103 (1)	–	
37	CH_3, 3-$NHCOCH_3$, 5-CH_3	9	HCl	−0.06	+0.2	10	117 (2)	49	–
38	CH_3, 3-NH_2, 5-CH_3, 3'-OCH_3	9	HCl	0.07	+1.7	1.25	125 (1)	–	
39	CH_3, 3-NH_2, 5,6-$(CH_3)_2$	9	HCl	−0.03	+1.9	5	87	–	
40	CH_3, 3-NH_2, 5,6-$(CH_3)_2$, 3'-OCH_3	9	HCl	0.14	+1.9	3	79	–	
41	CH_3, 3-NO_2, 5,3'-$(OCH_3)_2$	9	HCl-B	0.14	−2.2	25	66	39	–

[a] Salt form of the agent necessary to ensure water solubility for dosing. MsOH = methanesulfonic acid. Entries marked B have proved insufficiently soluble and have been administered as homogenized suspensions in vehicle B (aqueous methylcellulose). [b] Measure of lipophilic-hydrophilic balance from reverse phase partition chromatography.[8,9] [c] For monosubstituted variants the change produced in the pK_a of 9-aminoacridine by the acridine substituent employed.[17] [d] Optimum dose in mg/kg/day for ip drug administration to animals with ip implanted L1210. [e] Percentage increase in life span = ILS % = T/C (%) − 100. Standard inoculum of 10^5 L1210 cells implanted either intraperitoneally (ip), subcutaneously (sc), or intracerebrally (ic). All dosing ip qd 1-5. Numbers of 50-day survivors from that group receiving the optimum dose are provided in parentheses. [f] –, statistically significant life extension not observed. [g] Maximum tolerated dose not reached; higher doses may provide greater life extensions.

with the sc implant. Entries **22, 47** and **16, 48** provide further examples of the same effect. Scanning the active singly substituted variants shows that there are many examples where, with increasing R_m value, there is a drop in activity from that of the unsubstituted parent against ip L1210 but a similar change is not seen with the sc tumor: **2, 12; 2, 15; 2, 18; 2, 19; 2, 21; 20, 22; 20, 24.** Admittedly, certain of the substituents employed in these examples could be playing a role additional to merely increasing lipophilic character.

The combination of a 3-NO_2 and the acceptable 5- or 6-CH_3[6] in one molecule provides agents with marked activity against sc L1210 (**26, 27, 29–31**). It is difficult to see how this activity could have been anticipated from the effects of the singly substituted NO_2 (**13, 25**) or CH_3 (**16, 17, 23, 24**) congeners against either sc or ip L1210. The pattern of activity progression seen through the homologous 3-NO_2 alkanesulfonanilide derivatives (**50–52, 53–55**) suggests that some of the increased effectiveness of the 3-nitro-*x*-methyl-substituted variants against sc tumor is due to higher lipophilic character. Homologation of the highly sc active variant **31**, to provide **56**, furnishes an agent only moderately effective against either ip or sc tumor; presumably this is the resultant of excessive lipophilic character.[6]

No acridine derivative with an unprotected 2- or 3-NH_2 group has provided significant activity against sc implanted leukemia following ip administration (**10, 14, 32, 34, 36, 38–40, 57**). This does not appear solely due to the more hydrophilic nature of the NH_2 function. Certain examples (**32, 34, 38–40**) have R_m values and activity against ip L1210 as high as alternatively substituted agents which supply significant inhibition of sc tumor. Administration, via a tail vein, of variants **10** and **14** to mice with sc inoculated L1210 provides significant inhibition of tumor progression. Following ip administration these drugs must be sufficiently removed, either by excretion and/or deactivation, that adequate drug levels do not reach sc tumor site. Certain of the following SAR suggest ready metabolism is the probable cause. Amine functions, particularly a 3-NH_2, provide a valuable increase in dose potency and the latter is a component of the earlier re-

Table II. Agent, Structural Details, Physicochemical Properties, and L1210 Screening Data

No.	R in 1	Mp, °C	Formula	Analyses[a]	R_m	ΔpK_a[c]	O.D.[d]	L1210 ILS, %[e] ip	sc	ic
42	CH_2CH_3, 3′-OCH_3	258–259	$C_{22}H_{21}N_3O_3S$·MsOH	C, H, N, S	0.37	0.0	13	94	39	–[f]
43	$(CH_2)_2CH_3$, 3′-OCH_3	258–260	$C_{23}H_{23}N_3O_3S$·MsOH	C, H, N, S	0.56	0.0	18	88	53	26
44	$(CH_2)_3CH_3$, 3′-OCH_3	259–261	$C_{24}H_{25}N_3O_3S$·MsOH	C, H, N, S	0.64	0.0	63	59	39	–
45	CH_3, 3-$NHCOCH_2CH_3$	297–298	$C_{23}H_{23}N_4O_3S$·MsOH	C, H, N, S	0.07	0.0	40	108 (2)	49	–
46	CH_3, 3-$NHCO(CH_2)_2CH_3$	294–296	$C_{24}H_{25}N_4O_3S$·MsOH	C, H, N, S	0.29	0.0	45	67	31	–
47	CH_2CH_3, 3-Cl, 3′-OCH_3	268–269	$C_{22}H_{21}ClN_3O_3S$·MsOH	C, H, N, S	0.49	–0.7	13	85	55	27
48	CH_2CH_3, 3-CH_3	244–245	$C_{22}H_{22}N_3O_2S$·MsOH	C, H, N, S	0.30	+0.2	33	66	49	–
49	CH_2CH_3, 4-CH_4, 3′-OCH_3	234–235	$C_{23}H_{24}N_3O_3S$·MsOH	C, H, N, S	0.43	+0.2	9	79	49	31
50	CH_2CH_3, 3-NO_2	269–271	$C_{21}H_{18}N_4O_4S$[b]	C, H, N, S	0.12	2.1	20	118 (2)	57	–
51	$(CH_2)_2CH_3$, 3-NO_2	250–251	$C_{22}H_{20}N_4O_4S$[b]	C, H, N, S	0.34	–2.1	125	112 (3)	78	–
52	$(CH_2)_3CH_3$, 3-NO_2	218–219	$C_{23}H_{22}N_4O_4S$[b]	C, H, N, S	0.62	–2.1	100	72	61	–
53	CH_2CH_3, 3′-OCH_3, 3-NO_2	168–170	$C_{22}H_{20}N_4O_5S$[b]	C, H, N, S	0.30	–2.1	11	98 (3)	43	–
54	$(CH_2)_2CH_3$, 3′-OCH_3, 3-NO_2	124–125	$C_{23}H_{22}N_4O_5S$[b]	C, H, N, S	0.49	–2.1	50	106	54	–
55	$(CH_2)_3CH_3$, 3′-OCH_3, 3-NO_2	126–127	$C_{24}H_{24}N_4O_5S$·0.5H_2O[b]	C, H, N, S	0.61	2.1	38	80	47	–
56	CH_2CH_3, 3-NO_2, 5,6-$(CH_3)_2$, 3′-OCH_3	265–266	$C_{24}H_{24}N_4O_5S$[b]	C, H, N, S	0.44	1.7	60	71	43	–
57	CH_3, 2-NH_2, 3′-OCH_3	247–248	$C_{21}H_{20}N_4O_3S$·HCl	C, H, N, Cl	–0.13	+0.4	6	106	–	–
58	CH_3, 3-$NHCH_3$	215–217	$C_{21}H_{20}N_4O_2S$·HCl·H_2O	C, H, N, Cl	–0.01	+1.7	7	102 (2)	34	–
59	CH_3, 3-$N(CH_3)COCH_3$	194–196	$C_{23}H_{22}N_4O_3S$·HCl	C, H, N, Cl	0.06	0.0	67	118 (2)	32	–
60	CH_3, 3-$NHCH_3$, 3′-OCH_3	197–198	$C_{22}H_{22}N_4O_3S$·HCl·H_2O	C, H, N, Cl	0.17	+1.7	1.3	94 (2)	35	–
61	CH_3, 3-$NHCH_3$, 5-CH_3	218–221	$C_{22}H_{22}N_4O_2S$·HCl·H_2O	C, H, N, Cl	0.05	+1.9	1.2	103 (1)	31	–
62	CH_3, 3-$NHCH_3$, 5-CH_3, 3′-OCH_3	208–211	$C_{23}H_{24}N_4O_3S$·HCl·0.5H_2O	C, H, N, Cl	0.23	+1.9	0.62	68	–	–
63	CH_3, 3-$NHCH_3$, 5,6-$(CH_3)_2$	238–241	$C_{23}H_{24}N_4O_2S$·HCl	C, H, N, Cl	0.31	+2.1	5	66 (1)	27	–
64	CH_3, 3-$NHCH_3$, 5,6-$(CH_3)_2$, 3′-OCH_3	221–223	$C_{24}H_{26}N_4O_3S$·HCl·0.5H_2O	C, H, N, Cl	0.49	+2.1	1.25	64	–	–
65	CH_3, 2-NO_2, 6-Cl	302–303	$C_{20}H_{15}ClN_4O_4S$	C, H, N						
66	CH_3, 2-NH_2, 6-Cl	229–231	$C_{20}H_{17}ClN_4O_2S$·HCl·0.5H_2O	C, H, N, Cl	–0.18	–0.3	60	98 (2)	–	–
67	CH_3, 2-NO_2, 3-Cl	303–304	$C_{20}H_{15}ClN_4O_4S$·H_2O	C, H, N, Cl						
68	CH_3, 2-NH_2, 3-Cl	233–235	$C_{20}H_{17}ClN_4O_2S$·HCl·H_2O	C, H, N, Cl	–0.11	–0.3	60	103 (1)	39	–
69	CH_3, 2-NO_2, 3-CF_3, 3′-OCH_3	187–189	$C_{22}H_{17}F_3N_4O_5S$	C, H, N, S						
70	CH_3, 2-NH_2, 3-CF_3, 3′-OCH_3	210–213	$C_{22}H_{19}F_3N_4O_3S$·HCl·1.5H_2O	C, H, N, Cl	0.28	1.2	55	108 (2)	73	42
71	CH_3, 2-NH_2, 3-Br, 3′-OCH_3	215–217	$C_{21}H_{19}BrN_4O_3S$·HCl	C, H, N, Br	0.08	–0.3	12.5	90 (1)	31	–
72	CH_3, 2-NH_2, 3-Br, 5-CH_3	>360	$C_{21}H_{19}BrN_4O_2S$·HCl	C, H, N, Br	–0.04	–0.1	27	87 (3)	46	27
73	CH_3, 2-NH_2, 3-Br, 5-CH_3, 3′-OCH_3	>360	$C_{22}H_{21}BrN_4O_3S$·HCl	C, H, N, Br	0.07	0.1	23	83 (3)	46	27
74	CH_3, 2-NH_2, 3,4-$(CH_3)_2$, 3′-OCH_3	274–276	$C_{23}H_{24}N_4O_3S$·HCl	C, H, N, Cl	0.01	+0.8	40	61	27	–
75	CH_3, 3-Cl, 5-CH_3	213–215	$C_{21}H_{18}ClN_3O_2S$·HCl	C, H, N, Cl	0.21	0.5	60	76	33	–
76	CH_3, 3-Cl, 5-CH_3, 3′-OCH_3	212–214	$C_{22}H_{20}ClN_3O_3S$·HCl	C, H, N, Cl	0.40	0.5	15	57	–	–
77	CH_3, 3-Cl, 5-OCH_3	204–205	$C_{21}H_{18}ClN_3O_3S$·HCl·H_2O	C, H, N, Cl	0.15	–0.8	130	91	33	26
78	CH_3, 3-Cl, 5,3-$(OCH_3)_2$	204–206	$C_{22}H_{20}ClN_3O_4S$·HCl·H_2O	C, H, N, Cl	0.34	0.8	10	82	41	27
79	CH_3, 3,5$(CH_3)_2$	270–271	$C_{22}H_{21}N_3O_2S$·MsOH	C, H, N, S	0.16	+0.4	7.5	96	45	28
80	CH_2CH_3, 3,5-$(CH_3)_2$	265–266	$C_{23}H_{24}N_3O_2S$·MsOH	C, H, N, S	0.36	+0.4	10	58	39	29
81	CH_3, 3,5-$(CH_3)_2$, 3′-OCH_3	208–209	$C_{23}H_{23}N_3O_3S$·HCl	C, H, N, Cl						
		151–152	$C_{23}H_{23}N_3O_4S$·MsOH·H_2O	C, H, N, S	0.35	+0.4	4.5	97	50	29

82	CH_3, 3,5,3'-$(CH_3)_3$	169–170	$C_{23}H_{23}N_3O_2S$·MsOH	C, H, N, S	0.38	+0.4	29	82	50	29
83	CH_3, 4,5-$(CH_3)_2$	260–261	$C_{22}H_{21}N_3O_2S$·MsOH·H_2O	C, H, N, S	0.11	−0.6	100	96	52	53
84	CH_3, 4,5-$(CH_3)_2$, 3'-OCH_3	319–320	$C_{23}H_{23}N_3O_3S$·HCl	C, H, N, Cl						
		280–281	$C_{23}H_{23}N_3O_3S$·MsOH	C, H, N, S	0.28	−0.6	27	87	51	46
85	CH_2CH_3, 4,5-$(CH_3)_2$, 3'-OCH_3	252–253	$C_{24}H_{25}N_3O_3S$·MsOH	C, H, N, S	0.43	−0.6	24	81	76	46
86	CH_3, 4,5,3'-$(CH_3)_3$	291–292	$C_{23}H_{23}N_3O_2S$·HCl	C, H, N, Cl	0.31	−0.6	120	72	43	26
87	CH_3, 3,4-$(CH_3)_2$, 3'-OCH_3	242–243	$C_{23}H_{23}N_3O_2S$·MsOH	C, H, N, S	0.32	+0.4	11	79	34	—
88	CH_3, 3,4,3'-$(CH_3)_3$	226–227	$C_{23}H_{23}N_3O_2S$·MsOH	C, H, N, S	0.35	+0.4	27	57	29	—
89	CH_3, 3,4,6-$(CH_3)_3$	287–289	$C_{23}H_{23}N_3O_2S$·MsOH	C, H, N, S	0.27	+0.6	35	92	44	—
90	CH_3, 3,4,5-$(CH_3)_3$, 3'-OCH_3	255–256	$C_{25}H_{25}N_3O_3S$·MsOH·0.5H_2O	C, H, N, S	0.40	+0.6	11	58	38	—
91	CH_3, 3,4,5-$(CH_3)_3$	305 dec	$C_{23}H_{23}N_3O_2S$·HCl	C, H, N, Cl						
		256–258	$C_{23}H_{23}N_3O_2S$·MsOH	C, H, N, S	0.17	−0.4	44	82	44	33
92	CH_3, 3,4,5-$(CH_3)_3$, 3'-OCH_3	252–253	$C_{24}H_{25}N_3O_3S$·MsOH	C, H, N, S	0.35	−0.4	17	76	39	29

[a] Analyses for the elements indicated have been within ±0.4% of the theoretical figures required for the formula provided. [b] These weakly basic variants lose anion on drying and it was necessary to analyze the free bases to obtain satisfactory elemental analyses. Screening employed suspensions of the bases in aqueous methylcellulose. [c–f] See corresponding footnotes in Table I.

corded most dose potent agent of the series (**38**).[9] The desirability of retaining high potency has led to an examination of methods which will allow retention of acridinamine substituents and yet permit activity in screening tests against sc implanted tumor. N-Acetylation (**5, 33, 35, 37**) is effective in permitting activity against sc tumor but does not provide potency retention. N-Monomethylation (**58**) allows significant activity toward sc L1210 with higher potency. Both potency increasing 3-$NHCH_3$ and 3'-OCH_3 functions together provide an active and very potent isomer (**60**) which is able to inhibit sc implanted tumor. The 3-$NHCH_3$,5-CH_3,3'-OCH_3 congener **62**, requiring an optimum dose of only 0.6 mg/kg, must now be considered the most dose potent antileukemic agent of this series but certainly not the most active under the screening conditions used.

As amine function could be effectively shielded by N-methylation, it was conjectured that ortho ring substitution might also serve the same purpose. Earlier we had suggested that hydrophobic acridine 3-substituents might provide additional site binding[6,7] but that to capitalize on this it would be necessary to provide a counterbalancing hydrophilic substituent to obtain an agent having a close to optimum R_m value. Although the activity of the 2-NH_2 variants has generally been slightly depressed, we have attempted to employ this function as a hydrophilic unit in combination with hydrophobic 3-substituents. This has allowed a checking of our earlier conclusions[6,7] and also examined the possible protective effect of a substituent adjacent to a 2-NH_2 group. The 2-NH_2,6-Cl variant **66** requires the same optimum dose, has comparable lipophilic character, and provides equivalent activity against ip L1210 to that of the 2-NH_2,3-Cl isomer **68**. Only the latter, with the ortho-shielded amino group, is effective against sc implanted tumor. Similarly, a 2-NH_2 combined with a 3-Br (**71**) or 3-CF_3 (**70**) has provided good L1210 activity with the latter particularly effective against the sc tumor. A 2-NH_2,3-CH_3 variant, as in **74**, was marginally active against sc and only moderately so for ip L1210 implants. The activity of these 2-NH_2-substituted 3-CF_3 and 3-Br congeners (**70, 71**) against early ip L1210 is significantly higher than that of the parent 3-CF_3[7] and 3-Br (**15**) analogues, providing partial substantiation of our earlier views.[6,7] The protective effect of substitution ortho to a 2-NH_2 group is clearly seen.

Intracerebral L1210. Further screening of these agents using prompt, limited period dosage of animals with ic implanted L1210 provided yet shorter life extensions. Most earlier prepared agents proved inactive (Table I) and very few provided significant life extensions. There is little quantitative correspondence between the results obtained against ip and ic L1210. Current views on physicochemical properties necessary for blood–brain penetration by organic bases are low agent pK_a value and high lipophilic character.[15,16] The importance of a more lipophilic nature for ic activity is clear from the examples of Tables I and II but the results provide only limited evidence for the importance of low base strength. Inactivity of the more basic 3-$NHCH_3$ isomers (**58, 60–64**) might be construed as negative evidence for such an effect. However, the 3-NO_2 derivatives (**26, 27, 30, 31, 50–52**) are the least basic compounds and, while providing highest activity against sc tumor, are completely inactive against ic L1210 despite repeated testing. Possibly the 3-NO_2 congeners could act as precursors, more effectively delivering the dose potent 3-NH_2 compounds (**36–40**) to at least sc tumor site. These more strongly basic amines might not be expected to

penetrate readily to intracerebral spaces with the example provided by the 3-$NHCH_3$ variants (**60–64**).

Ionization constants for many of the acridines prepared in this laboratory have been measured in aqueous solution. The more insoluble examples, particularly the nitro group containing congeners, cannot be so measured. To furnish a complete comparative range, ΔpK_a figures, taken from Albert's extensive work of substituent effects on the pK_a of 9-aminoacridine,[17] have been provided (Tables I and II). These ΔpK_a units have been used in purely additive fashion; available measured examples show that trends in changing base strength are reasonably predicted in this fashion.

Acridine ring methylation permits fine adjustment of both agent lipophilic character and base strength; a single CH_3 provides an increase in base strength ($\Delta pK_a = +0.2$) but steric hindrance to proton approach by 4,5-disubstitution produces a decrease ($\Delta pK_a = -0.6$).[17] The quite reasonable ic activity of the 4,5-$(CH_3)_2$ variants (**83–85**), in comparison with the base strengthening 3,5-substituted examples (**79–81**), may then reflect the differing pK_a values. Similar effects are encountered in the 3,4,6- (**89, 90**) and the 3,4,5-$(CH_3)_3$ (**91, 92**) isomers.

Alternatively, it could be suggested that the presence of a 4-CH_3 and, to a lesser extent, a 4-OCH_3 group assists drug translocation, possibly by hindering the approach of acridine cationic ring nitrogen to encountered diversionary anionic sites.[18] The ic activity of acridines with a single base strengthening 4-CH_3 (**17, 24**; cf. 3-CH_3 isomers **16, 23**) and a 4-OCH_3 group (**18**; cf. **11**) would support this view. The somewhat higher activity of the 4,5-$(CH_3)_2$ (**83–85**) and the 3,4,5-$(CH_3)_3$ (**91, 92**) variants would then reflect the presence of two such equivalently placed methyl groups. Additional support for this view stems from addition of a 4-CH_3 to the ic inactive 2-NH_2,3-Br derivative **71** to provide agents with small ΔpK_a decreases from the parent but effectiveness against ic tumor (**72, 73**); an increase in activity against sc L1210 is seen at the same time.

A similar beneficial effect of a 4-CH_3 group for activity against sc L1210 could also be proposed. Such a methyl group does not provide the full increment in R_m values expected from those seen with 3-CH_3 substitution (**16, 23**) or on homologation of the alkanesulfonamide residue (**2–4, 5–9**). Presumably this results from the effect of the adjacent acridine ring nitrogen; neighboring polar functions are known to modulate π values.[19] Despite being less lipophilic the 4-CH_3 congeners (**17, 24**) appear more active against sc L1210 than the corresponding 3-isomers (**16, 23**). Such an effect could provide a partial explanation for the excellent sc activity of the 3-nitro variants (**26, 27, 30, 31**) containing a 4- (5-) CH_3 group and the lesser activity of the isomeric 3-NO_2,6-CH_3 variants (**28, 29**).

It was earlier suggested that a 4-CH_3 group appended to 9-aminoacridine was beneficial for antibacterial activity[20] and possibly decreased adsorption to wasteful sites.[18]

Discussion

The screening results presented, obtained within the confines of a single congeneric series of drugs, provide an excellent commentary on the pitfalls inherent in the use of any screening system. When using a single target cell line and a standardized route and schedule of administration, variation of the site of tumor implantation causes a different "best" member of the drug series to be selected for each implantation site used. In general, it appeared that for good activity against tumor implanted remotely from ip administration site a drug should be more lipophilic than that found optimal for ip dosage of ip implanted tumor.[6]

It is well known that apparent effectiveness of a drug in an in vivo test system depends on, among other factors, route of drug administration and anatomic location of target species. We have shown that there is not a constant proportionality in such changes in effectiveness within members of a single drug series. The questions then requiring answers are which combination of drug administration route and site location will rank members of a congeneric series most effectively for preclinical selection and which combination provides the medicinal chemist with adequate quantitative measures of drug selectivity for deriving quantitative SAR? If there is an apparent change in effectiveness with changing drug administration site in an experimental test system, a similar result can be expected in patients; the combination most closely paralleling clinical practice would then provide best preclinical ranking. For example, if leukemic patients will receive drug intravenously, for treatment of the advanced and disseminated disease, then ranking tests should employ iv drug administration to animals with advanced and disseminated disease. The medicinal chemist's wish to provide the most effective clinical agent will dictate acceptance of measures obtained from the same ranking system for derivation of SAR. However, the observed SAR when tumor has been implanted at varying locations are different. These SAR are clearly a resultant balancing of pharmacokinetic properties, influencing drug migration to tumor cells as well as intrinsic ability of drug to penetrate those cells and interact with site of action. It is clear that any tumor inhibition observed in vivo results from a compromise and the SAR available to the medicinal chemist invariably represent a mixture of tumor and host impressed factors. To use the term compromise inevitably implies that less than the maximum attainable effect has been accepted. The medicinal chemist needs information on how altering physicochemical parameters change drug pharmacokinetic properties. If such information becomes available, it may prove possible to divorce those physicochemical features necessary for pharmacokinetic properties from those required for tumor selectivity. From such knowledge it may then prove possible to arrange a better overall compromise and therefore obtain more effective agents.

There may be additional compromises made when experimental (and clinical) solid tumor systems are the target. It could be questioned, what are the drug physicochemical properties necessary to distribute to, pervade, and blockade the active cellular sites in a large primary tumor? Are these the same as those required for the blood borne micrometastases and tumor cells? If there is meningeal involvement, what optimum drug properties are necessary to reach and effectively inhibit the larger cerebral tumor masses as well as the disseminated cells?

It could be conjectured from the results provided (Tables I and II) that to effectively combat advanced and disseminated L1210 with members of this series, no one drug, i.e., compound with a single set of physicochemical properties, would provide effective control and that a combination of two or more could provide superior results. As a logical extension of the above ideas we have suggested that certain multiple drug-masking (latentiation) schemes may permit the modification of the pharmacokinetic properties of a single agent to approximate more closely those necessary for effective inhibition of a disseminated cancer.[21] This scheme envisages the use of a series of masking functions linearly linked to a drug. In vivo, as

Table III

Benzoic acid substituents	Yield, %	Mp, °C	Formula	Analyses
4-Chloro-5-nitro-2-phenylamino-	69	242-243[a]	$C_{13}H_9ClN_2O_4$	C, H, N, Cl
4-Chloro-2-(4-nitrophenylamino)-	32	235-236[b]	$C_{13}H_9ClN_2O_4$	C, H, N, Cl
2-(4-Nitro-3-trifluoromethylphenylamino)-	28	182-183	$C_{14}H_9F_3N_2O_4$	C, H, N
4-Methyl-2-(2-methylphenylamino)-	72	197-198	$C_{15}H_{15}NO_2$	C, H, N
2-(4-Acetamido-2,3-dimethylphenylamino)-	64	288-289	$C_{17}H_{18}N_2O_3$	C, H, N
2-[3-(*N*-Methylbenzenesulfonamido)phenylamino]-	59	198-199	$C_{20}H_{18}N_2O_4S$	C, H, N, S
4-(*N*-Methylbenzenesulfonamido)-2-(2,3-dimethylphenylamino)-	33	186-188	$C_{22}H_{22}N_2O_4S$	C, H, N, S
5-Acetamido-4-bromo-2-phenylamino-	63	277-279	$C_{15}H_{13}BrN_2O_3$	C, H, N, Br
5-Acetamido-4-bromo-2-(2-methylphenylamino)-	37	270-271	$C_{16}H_{15}BrN_2O_3$	C, H, N, Br

[a] Lit.[22] mp 240 °C. [b] Lit.[23] mp 235 °C.

each masking group is sequentially removed a new drug derivative is liberated and, reflecting its physicochemical properties, will have a particular physiologic disposition pattern, half life, ability to penetrate the blood–brain barrier, etc. For such schemes, where there is a release of core active agent via a cascade of sequenced events, we have suggested the term cascade latentiation. Such cascade sequences could, in effect, furnish a series of drugs each with physicochemical properties which could provide in total a desirable set of pharmacokinetic properties.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Analyses were performed by Dr. A. D. Campbell, Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal melting point apparatus with the makers' supplied stem corrected thermometer; melting points are as read. NMR spectra were obtained on a Varian A-60 spectrometer (Me_4Si). Ir spectra (KBr) were recorded using a Beckmann 237 Infracord. Uv spectra were recorded on a Shimadzu UV-200.

To monitor the progress of reactions, purification of products, etc., TLC on SiO_2 (Merck SiO_2, F_{254}) was used. R_m values for all described agents have been measured in the reversed phase partition chromatographic system recently described.[8,9]

2,4-Dibromo-5-acetamidobenzoic Acid. Finely ground 2,-4-dibromo-5-methylacetanilide (43.1 g, 0.14 mol) was dissolved in a mixture of Py (120 ml) and H_2O (90 ml) by stirring and boiling. The flask and contents were cooled slightly and $KMnO_4$ (89 g, 0.56 mol) was added portionwise to the well-stirred solution as permitted by the vigor of the reaction. Finally, the heterogeneous mixture was heated under reflux conditions until all $KMnO_4$ was consumed, MnO_2 removed on a Celite pad, and this rinsed with boiling 60% Py–H_2O (50 ml). Concentration of the filtrate in vacuo followed by acidification (0.5 N HCl) of the cooled residue provided crude product which was collected, washed with H_2O, and then stirred into 10% $KHCO_3$ (200 ml). Starting material was recovered by filtration and acidification of the filtrate provided the required acid. Crystallization (EtOH–H_2O) afforded pure product as colorless needles of mp 267–268 °C (26.9 g, 57%). Anal. ($C_9H_7Br_2NO_3$) C, H, N, Br.

***N*-(4-Butanamido-3-methoxyphenyl)ethanesulfonamide** was prepared from equimolar quantities of *N*-(4-amino-2-methoxyphenyl)butanamide[7] and ethanesulfonyl chloride in Py solution, exactly as done before for preparation of the corresponding methanesulfonamide.[7] Pure product separated from EtOH in colorless needles of mp 135–136 °C (73% yield). Anal. ($C_{13}H_{20}N_2O_4S$) C, H, N, S. The corresponding propanesulfonamide [mp 122–123 °C, 69% yield. Anal. ($C_{14}H_{22}N_2O_4S$) C, H, N, S] and butanesulfonamide [mp 121–122 °C, 74% yield. Anal. ($C_{15}H_{24}N_2O_4S$) C, H, N, S] were prepared in equivalent fashion.

Methyl 4-Benzenesulfonamido-2-chlorobenzoate. Benzenesulfonyl chloride (14.2 ml, 0.115 mol) was added in dropwise fashion to an ice-cooled, stirred solution of methyl 4-amino-2-chlorobenzoate (19.3 g, 0.104 mol) in Py (40 ml) so that the temperature remained below 5 °C. The mixture was heated on the steam bath for 30 min and then concentrated in vacuo and the residue shaken with H_2O. The resulting solid was collected, washed with H_2O, and crystallized from MeOH–H_2O (below 50 °C) and then C_6H_6–petroleum ether. Pure product was obtained as colorless plates of mp 138–140 °C (31.0 g, 91%). Anal. ($C_{14}H_{12}ClNO_4S$) C, H, N, Cl.

Methyl 2-Chloro-4-(*N*-methylbenzenesulfonamido)-benzoate. A mixture of the aforementioned compound (26.7 g, 0.082 mol), Me_2SO_4 (8.20 ml, 0.086 mol), anhydrous K_2CO_3 (12 g), and dry Me_2CO (70 ml) was heated at reflux temperature, while stirring, for 1.5 h. Removal of inorganic salts and evaporation left an oil which was dissolved in hot C_6H_6 (60ml) and the solution diluted with petroleum ether (180 ml). The oil separating solidified on seeding. The crude product was washed with petroleum ether and dried, providing product (25.1 g, 90%) homogeneous to TLC. Crystallization from C_6H_6–petroleum ether provided an analytical sample of mp 65–66 °C. Anal. ($C_{15}H_{14}ClNO_4S$) C, H, N, Cl.

2-Chloro-4-(*N*-methylbenzenesulfonamido)benzoic Acid. The above methyl ester was dissolved in a twofold excess of 1 N KOH in 85% MeOH–KOH by warming and the solution allowed to stand at room temperature for 1 h. After removal of MeOH in vacuo on a steam bath, the residue was diluted with water and clarified and crude acid precipitated with HCl. Crystallization from C_6H_6–petroleum ether provided pure product as colorless prisms of mp 134–135 °C (92% yield). Anal. ($C_{14}H_{12}ClNO_4S$) C, H, N, Cl.

The following substituted benzoic acid derivatives (Table III) were prepared by Jourdan–Ullmann[10] condensations between equimolar quantities of the requisite 2-halobenzoic acid and substituted aniline components employing the experimental modifications listed earlier[6] and equivalent work-up of reaction mixtures.

2-Nitro-3-trifluoromethyl-9(10*H*)-acridone. To a well-stirred, ice–water cooled suspension of 2-(4-nitro-3-trifluoromethylphenylamino)benzoic acid (0.05 mol) in C_6H_6 (50 ml) were added successively Py (0.05 mol) and $SOCl_2$ (0.06 mol). There was rapid reaction and after 30 min of stirring the mixture was concentrated in vacuo at room temperature to half volume. Further Py (0.05 mol) and piperidine (0.12 mol) were then added and the mixture was heated on a steam bath under reflux conditions for 2 h. H_2O was added to the reaction mixture and the separated C_6H_6 layer was washed successively with 2 N HCl, H_2O, 10% $KHCO_3$, and H_2O and then dried (Na_2SO_4) and solvent was removed in vacuo. The residual pale-yellow piperidide derivative was crystallized from C_6H_6–petroleum ether: mp 187–189 °C (87% yield). Anal. ($C_{19}H_{18}F_3N_3O_3$) C, H, N. This amide (0.03 mol) was heated with $POCl_3$ (25 ml) on a steam bath, until a clear solution resulted, and then for 1 h further. After removal of excess $POCl_3$ in vacuo, HOAc (50 ml) and concentrated HCl (10 ml) were added to the residue. After 2 h of heating at 100 °C, solvents were removed in vacuo and H_2O was added. The solid crude acridone was collected, washed well with H_2O, dried, and then crystallized repeatedly from DMF–MeOH until homogeneous to TLC. Pure acridone (Table IV) was obtained as yellow needles in 63% overall yield.

3-Methylamino-5-methyl-9(10*H*)-acridone. *N*-[3-(*N*-Methylbenzenesulfonamido)phenyl]benzamide (0.03 mol) was suspended in $SOCl_2$ (50 ml) containing DMF (0.2 ml) and the suspension stirred until a clear solution resulted. After a further 24 h at room temperature excess $SOCl_2$ was removed in vacuo at 70 °C and the formed imidoyl chloride[9] stored in an evacuated dessicator over KOH pellets. Methyl *o*-cresotinate[9] (0.03 mol), dissolved in dry DMF (7.5 ml), was cooled in an ice–salt mixture

Table IV. Substituted 9(10*H*)-Acridones

Substituents	Mp, °C	Formula	Analyses
3-$NHCH_3$	280 dec	$C_{14}H_{12}N_2O$	C, H, N
3-$N(CH_3)COCH_3$	261-262	$C_{16}H_{14}N_2O_2$	C, H, N
3-$NHCH_3$, 5-CH_3	288-290	$C_{15}H_{14}N_2O$	C, H, N
3-$N(CH_3)COCH_3$, 5-CH_3	285-288	$C_{17}H_{16}N_2O_2$	C, H, N
3-$NHCH_3$, 5,6-$(CH_3)_2$	315 dec	$C_{16}H_{16}N_2O$	C, H, N
3-$N(CH_3)COCH_3$, 5,6-$(CH_3)_2$	327 dec	$C_{18}H_{18}N_2O_2$	C, H, N
2-NO_2, 3-CF_3	>360	$C_{14}H_7F_3N_2O_3$	C, H, N
2-NH_2, 3-CF_3	338 dec	$C_{14}H_9F_3N_2O$	C, H, N
2-$NHCOCH_3$, 3-CF_3	>360	$C_{16}H_{11}F_3N_2O_2$	C, H, N
2-$NHCOCH_3$, 3-Br	277-279	$C_{15}H_{11}BrN_2O_2$	C, H, N, Br
2-$NHCOCH_3$, 3-Br, 5-CH_3	>360	$C_{16}H_{13}BrN_2O_2$	C, H, N, Br
3,4,5-$(CH_3)_2$	237-238	$C_{16}H_{15}NO$	C, H, N
2-$NHCOCH_3$, 3,4-$(CH_3)_2$	>360	$C_{17}H_{16}N_2O_2$	C, H, N

and NaH (50% dispersion in oil, 0.03 mol) was added as permitted by the vigor of reaction. The mixture was stirred at room temperature overnight to allow last traces of NaH to react. The crude imidoyl chloride, dissolved in C_6H_6 (30 ml), was added to the solution of sodium methyl *o*-cresotinate at 0 °C and the mixture stirred at this temperature for 12 h. After 30 min of heating at 100 °C solvents were removed in vacuo at steam bath temperature, HOAc (1 ml) was added, and crude product precipitated with H_2O. Two crystallizations from MeOH provided TLC homogeneous 2-methoxycarbonyl-6-methylphenyl *N*-[3-(*N*-methylbenzenesulfonamido)phenyl]benzimidate of mp 127–127.5 °C (68%). Anal. ($C_{29}H_{26}N_2O_5S$) C, H, N, S. To this imidate ester (0.04 mol) was added Dowtherm A (0.75 ml/g) and the whole mixture heated to reflux temperature until TLC monitoring demonstrated that thermal rearrangement was complete. Cooling and precipitation with petroleum ether afforded crude *N*-(2-methoxycarbonyl-6-methylphenyl)-*N*-[3-(*N*-methylbenzenesulfonamido)phenyl]benzamide which, after crystallization from MeOH, had mp 157–158 °C (73%). Anal. ($C_{29}H_{26}N_2O_5S$) C, H, N, S. Ester function was saponified by solution in 1 N KOH in 85% MeOH (60 ml) and heating under reflux conditions for 30 min. After removal of MeOH in vacuo and dilution with H_2O, crystalline acid was precipitated from the clarified solution by addition of HCl. The acid was well washed with water, dried, and added to 92% w/w H_2SO_4 (30 ml) at room temperature. After stirring at this temperature for 24 h the clear solution was heated at 100 °C for 2 h. Cooling and then dilution with H_2O (200 ml) provided a turbid solution which was clarified and then crude acridone precipitated by basification with NH_3. The precipitated yellow acridone was repeatedly crystallized from DMF–H_2O until homogeneous to TLC (67% yield) (Table IV).

3,4,5-Trimethyl-9(10*H*)-acridone was prepared by equivalent procedures. Reaction, as above, of sodium methyl *o*-cresotinate (0.06 mol) and the crude imidoyl chloride from *N*-(2,3-dimethylphenyl)benzamide (0.06 mol) provided 2-methoxycarbonyl-6-methylphenyl *N*-(2,3-dimethylphenyl)benzimidate, mp 100–101 °C (59%). Anal. ($C_{24}H_{23}NO_3$) C, H, N. Thermal rearrangement of this product in refluxing Dowtherm, as above, provided *N*-(2-methoxycarbonyl-6-methylphenyl)-*N*-(2,3-dimethylphenyl)benzamide of mp 152–153 °C (87%). Anal. ($C_{24}H_{23}NO_3$) C, H, N. Following saponification of ester function as before the resulting acid (0.02 mol) was cyclized to the desired acridone by solution in commercial polyphosphoric acid (70 g) at 140 °C for 30 min. Crystallization from HOAc provided pure acridone as pale-yellow needles in 72% yield (Table IV).

Conditions for reduction of nitroacridones and acetylation of aminoacridones have been detailed earlier.[4-9]

Biological Testing. 10^5 L1210 cells were inoculated either intraperitoneally, subcutaneously above the right axilla, or intracerebrally through a temporal fissure into 18.5–22.5-g C_3H/DBA_2 F_1 hybrid mice. Ip drug treatment started 24 h later and continued for 5 days. An animal dose was contained in a volume of 0.2 ml. Dose levels were separated by 0.18 log dose units and there were six animals per dose level and one control group for every six test groups.

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